Cholinergic dysfunction and amnesia in patients with Wernicke-Korsakoff syndrome: a transcranial magnetic stimulation study

Cholinergic dysfunction and amnesia in patients with Wernicke-Korsakoff syndrome: a TMS study

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Abstract

The specific neurochemical substrate underlying the amnesia in patients with Wernicke-Korsakoff syndrome (WKS) is still poorly defined. Memory impairment has been linked to dysfunction of neurons in the cholinergic system. A transcranial magnetic stimulation (TMS) protocol, the short latency afferent inhibition (SAI), may give direct information about the function of some cholinergic pathways in the human motor cortex. In the present study we measured SAI in eight alcoholics with WKS and compared the data with those from a group of age-matched healthy individuals; furthermore, we correlated the individual SAI values of the WKS patients with memory and other cognitive functions. Mean SAI was significantly reduced in WKS patients when compared with the controls. The low score obtained in the Rey Complex Figure delayed recall test, the Digit Span subtest of the Wechsler Adult Intelligence Scale – Revised (WAIS-R) and the Corsi's Block Span subtest of the WAIS-R documented a severe impairment in the anterograde memory and short-term memory. None of the correlations between SAI values and these neuropsychological tests reached significance. We provide physiological evidence of cholinergic involvement in WKS. However, this putative marker of central cholinergic activity did not correlate positively with the memory deficit in our patients. These findings suggest that the cholinergic dysfunction does not account for the memory disorder and damage to the cholinergic system is not sufficient to cause a persisting amnesic syndrome in WKS.

Key words: Wernicke-Korsakoff syndrome, amnesia, transcranial magnetic stimulation, short latency afferent inhibition, cholinergic function

Introduction

The Wernicke-Korsakoff syndrome (WKS) is a neuropathological term which encompasses two clinical syndromes in thiamine-deficient alcoholics and non-alcoholics, Wernicke encephalopathy and the associated amnesic syndrome, Korsakoff psychosis. Wernicke encephalopathy is characterised by eye and gait disorders and mental confusion, and can lead to the profound and permanent amnesia known as Korsakoff psychosis. The clinical diagnosis of Korsakoff psychosis has only recently standardized with the clinical amnesic syndrome characterized by persistent anterograde memory loss and preserved semantic memory, intelligence and learned behaviour (Kopelman 1995; Caine et al. 1997).

Although there are several comprehensive descriptions of the neuropathology of Wernicke encephalopathy (Victor et al. 1989; Harper and Kril 1990) the specific neural substrate underlying the amnesia in WKS is also poorly defined. Central cholinergic mechanisms have been implicated in cortical activation and memory. The basal forebrain cholinergic neurons (BFCNs) provide the major cholinergic input to hippocampal and cortical regions and are believed to modulate cognitive and attentional processes (Kasa et al. 1997; Bartus 2000).

Cell counting has shown that WKS could be associated with a reduction of BFCNs, including the nucleus basalis of Meynert, the major source of cortical acetylcholine (Ach) (Arendt et al. 1988). Mayes and co-workers (1998) made morphometric measurements of BFCNs of two cases of WKS; in both cases, the post-mortem study showed a decrease in the number or nucleolar volume of magnocellular neurons in the nucleus basalis of Meynert. However, although cholinergic involvement in the amnesic syndrome is widely cited in the literature on WKS, the studies supporting the hypothesis have lacked appropriate controls (Arendt et al. 1988, 1995). A neuro.pathologic study showed that cell loss in the cholinergic nucleus basalis is minor (Cullen et al. 1997). Whereas neurons in the nucleus basalis are at risk in thiamine

deficient alcoholic patients, cell loss is minor and does not account for the profound memory disorder.

Thus, the current evidence from post-mortem and in vivo studies on cholinergic involvement in WKS was inconclusive. Also treatments for WKS remain elusive and the role of the cholinergic system in WKS needs to be further investigated in view of implications for treatment with cholinergic agents. It is well established that acetylcholinesterase (AchE) inhibitors offer a partial benefit in Alzheimer's dementia (AD) and other dementias characterized by memory deficit. Theoretically, AchE inhibitors might similarly prove to be at least partially useful in WKS. Kopelman and Corn (1998) investigated the effect of cholinergic blockade on a spectrum of memory functions and found a pattern of deficit that corresponded more closely to that seen in WKS than that in AD. Some case reports of alcohol-related WKS treated with AchE (Angunawela and Barker 2001; Cochrane et al. 2005) suggested promising results. However, another study of donepezil in the treatment of seven patients with non-alcoholic WKS (Sahin et al. 2002) showed no benefit over placebo, and recently Luykx and colleagues (2008) reported that rivastigmine may not be effective in restoring memory in WKS patients.

In vivo demonstration of cholinergic deficit in AD and other dementias was recently provided using a transcranial magnetic stimulation (TMS) technique that may held information about the function of some cholinergic circuits in the human brain (Di Lazzaro et al. 2002, 2006; Nardone et al. 2006; Manganelli et al. 2008) This technique relies on short latency afferent inhibition (SAI) of the motor cortex (Tokimura et al. 2000).

The present study examined SAI in patients with WKS; furthermore, we correlated this putative marker of central cholinergic activity with memory and other cognitive functions.

Materials and methods

Patients

The study included eight patients (six men and two women, mean age 54.4 years, range 35-62) with alcohol induced persisting amnesic disorder (WKS; DMS-IV) (American Psychiatric Association, 1994) and 10 age-matched neurologically healthy controls (eight men and two women, mean age 53.0 years, range 33-65 years). Seven patients and nine control subjects were right-handed.

At the time of neurophysiological examination, MRI was unremarkable in two patients and showed atrophy of the mammillary bodies in six patients. Patients with brain lesions involving brain regions other than the mammillary bodies were excluded from the study. Exclusion criteria also included: evidence of concomitant dementia such as AD, frontotemporal, vascular, or reversible dementias; evidence of concomitant extra-pyramidal symptoms; evidence of depression; other psychiatric diseases, epilepsy, drug addiction; current or previous uncontrolled or complicated systemic diseases or traumatic brain injuries. Nerve conduction studies excluded peripheral neuropathies in all patients. All the selected WKS patients were able to understand and carry out the simple tasks required for this electrophysiological study, such as to contract a hand muscle or to keep fully relaxed.

None of the patients were treated with anticholinergic drugs before the study. Administration of all drugs that affect motor cortex excitability in patients and control subjects was discontinued at least two weeks before the study.

A neuropsychological examination was performed between 8 weeks and 3 months after onset of the disease using the following tests: the Mini-Mental State Examination (MMSE), the Rey Complex Figure, the Wechsler Adult Intelligence Scale (WAIS) Information subtest, the Digit Span subtest of the WAIS – revised (WAIS-R), the Corsi's Block Span subtest of the WAIS-R and the Gollin Incomplete Pictures Test.

The main demographic characteristics and the performance of each patient on these neuropsychological tests are reported in the Table 1. The global level of cognitive functions was slight reduced or within the normal range. As expected, the poor performances on the Rey Complex Figure delayed recall test, on the WAIS-R Digit Span and Corsi's Block Span subtests revealed a severe impairment of anterograde episodic memory, short-term verbal memory and short term visual/spatial memory. The good performance in the immediate recall test on the Rey Complex Figure indicates a relative preservation of visuospatial/constructional abilities and the good performance on the Gollin test could be explained by the preservation of immediate and non-declarative memory. The semantic memory storage was also preserved, as proved by the score obtained in the WAIS Information subtest.

Patients provided informed consent before participation in this study, which was performed according the Declaration of Helsinki and approved by the institutional Ethics Committee.

Transcranial magnetic stimulation

TMS was performed using a High-power Magstim 200 magnetic stimulator (Magstim Co., Whitland, Dyfed, UK). A figure-of-eight coil with external loop diameters of 9 cm was held over the motor cortex at the optimum scalp position to elicit motor responses in the first dorsal interosseous (FDI) muscle. The dominant hemisphere was selected for stimulating patients and healthy subjects. The induced current flow in a postero-anterior direction. MEPs were recorded via two 9 mm diameter Ag-AgCl electrodes with the active electrode applied over the motor point of the muscle and the reference on the metacarpophalangeal joint of the index finger. MEPs were amplified and filtered (bandwidth 3-3000 Hz) by D150 amplifiers (Digitimer, Welwyn Garden City, Herfordshire, UK).

SAI was studied using the recently described technique (Tokimura et al. 2000).

Conditioning stimuli were single pulses (200 μs) of electrical stimulation (with the cathode positioned proximally) applied through bipolar electrodes to the median nerve at the wrist. The intensity of the conditioning stimuli was set at just over motor threshold for evoking a visible twitch of the thenar muscles. The intensity of the test cortical magnetic shock was adjusted to evoke a muscle response in relaxed FDI with an amplitude of approximately 1mV peak-to-peak. The conditioning stimulus to the peripheral nerve preceded the test magnetic cortical stimulus. Interstimulus intervals (ISIs) were determined relative to the latency of the N20 component of the somatosensory evoked potential evoked by stimulation of the median nerve. The active electrode for recording the N20 potential was attached 3 cm posterior to C3 (10-20 system), and the reference was 3 cm posterior to C4. Five hundred responses were averaged to identify the latency of N20 peak. ISIs from the latency of the N20 component plus 2 ms to the latency of the N20 component plus 8 milliseconds were investigated in steps of 1 ms.

Five repeats were delivered for cortical magnetic stimulation alone and for conditioned stimulation at each ISI in pseudo-randomised order. The amplitude of the conditioned MEP was expressed as a percentage of the amplitude of the test MEP. The percentage inhibition of the conditioned responses at the seven different ISIs was averaged to obtain a grand mean of SAI. Subjects were given audio-visual feedback at high gain to assist in maintaining complete relaxation.

In addition to SAI, we evaluated the following TMS parameters: the resting and active motor threshold of MEP; the central motor conduction time (CMCT); the short latency intracortical inhibition (SICI) and intracortical facilitation (ICF) to paired TMS.

Resting motor threshold (RMT) was defined as the minimum stimulus intensity that produced a liminal motor evoked response (about 50 μV in 50% of 10 trials) at rest. Active motor threshold (AMT) was defined as the minimum stimulus intensity that produced a liminal

motor evoked response (about 200 μV in 50% of 10 trials) during isometric contraction of the tested muscle at about 10% maximum.

Central motor conduction was calculated by subtracting the peripheral conduction time from spinal cord to muscles from the latency of responses evoked by cortical stimulation with the formula: MEP latency – (F latency + M latency – 1)/2 (Rossini et al. 1994).

Intracortical inhibition and facilitation were studied using the technique of Kujirai et al. (1993).

Using a Bistim module, two magnetic stimuli were given through the same stimulating coil over the motor cortex and the effect of the first (conditioning) stimulus on the second (test) stimulus was investigated. The conditioning stimulus was set to 90% AMT. The second, test, shock intensity was adjusted to evoke a muscle response in relaxed FDI with an amplitude of approximately 1 mV, peak-to-peak.

The timing of the conditioning shock was altered in relation to the test shock. Inhibitory interstimulus intervals (ISIs) of 3 ms and facilitatory ISIs of 10 ms were investigated. The amplitudes of motor evoked potentials evoked by single stimuli were comparable. Ten stimuli were delivered at each ISI. For these recordings, muscle relaxation is very important and the subject was given audiovisual feedback at high gain to assist in maintaining complete relaxation. The presentation of conditioned and unconditioned trials was randomised. The amplitude of the conditioned EMG responses was expressed as the percentage of the amplitude of the test EMG responses. The amplitude of the conditioned responses were averaged obtaining grand mean amplitudes of the inhibitory and of the facilitatory ISIs.

To clarify a possible spinal or peripheral contribution on the motor cortex excitability parameters, supramaximal stimulation (0.2-milliseconds square-wave constant current pulsies) of the ulnar nerve at the wrist was used to assess spinal and peripheral motor excitability. While FDI was relaxed, the peak-to-peak amplitude of F waves (average, 20 trials) and CMAP (maximum, 3 trials) were determined.

Statistical analysis

The electrophysiological parameters of the WKS patients were analysed separately and compared with those of the control subjects by means of Mann–Whitney tests. The level of significance was set at 0.05.

The relation between different variables, including the statistical comparison between the SAI and the 8 examined neuropsychological response measures, were performed by using the Spearman rank correlation and the Pearson product moment correlation coefficients.

Results

The neurophysiological data are summarized in the Table 2.

The mean amount of SAI was significantly smaller in the WKS patients (mean responses reduced to 64.3 % ± 14.2 of test size) than in normal controls (mean responses reduced to 44.7 % ± 9.4 % of test size; $P < 0.05$, Mann–Whitney test, $N_1 = 8$, $N_2 = 10$).

RMT, AMT, CMCT, SICI and ICF did not differ significantly between WKS subjects and control subjects ($P > 0.05$, Mann–Whitney test, $N_1 = 8$, $N_2 = 10$).

SAI showed a significant correlation only with the WAIS Information subtest (Pearson's correlation coefficient equal to -0.6); there were no positive correlations between SAI and the remaining neuropsychological tests performed (Table 3). Moreover, SAI did not correlate significantly with age, sex, and presence or absence of mammillary bodies atrophy ($P > 0.01$; Spearman's r).

Discussion

We first demonstrated excitability changes in those cholinergic cortical networks that are involved in SAI in patients with WKS. The number of patients with abnormal SAI conceivably reflects the percentage of subjects with a significant cholinergic dysfunction among the patients with a clinical diagnosis of WKS.

The common factor underlying the development of WKS syndrome is almost certainly due to depletion of thiamine. It has been reported that thiamine deficiency may damage the cholinergic system as a result of a complex interaction between cellular, neurochemical and metabolic properties (Witt, 1985). Thiamine pyrophosphate (TPP), the active form of thiamine, is involved in three enzymatic reactions essential for the metabolism of glucose and the production of neurotransmitters, including that of Ach. The inhibition of TPP-dependent pyruvate decarboxylase may cause an impairment in the synthesis of Ach (Gibson et al. 1975). Moreover, it is reported that cholinergic-rich brain transplants or cholinergic drugs reverse alcohol-induced memory deficits in animals (Hodges et al., 1991; Arendt et al. 1995).

The most salient finding of our study is that SAI deficit did not reflect the severity of cognitive dysfunction; in particular, the cholinergic involvement does not seem to be correlated with the severity of memory disturbances.

Therefore, we provide further evidence that the correlation between the decrease in cholinergic function and the cognitive decline is not as clearcut as has been assumed. Overall, the notion that Ach plays a pivotal role in learning and memory processes is likely to be overstated. The cholinergic nucleus basalis is an exclusive site of neurofibrillary degeneration in thiamine deficient alcoholic patients (Cullen et al. 1997) but could have a more circumscribed role in attention (Voytko et al. 1994; Blockland, 1996). The primate cholinergic basal forebrain seems to be more specifically involved in attentional processes

than in learning and memory processes. On the other hand, considering the complexity of the neuronal networks in the brain, it is unlikely that one neurotransmitter regulates such a complex mechanism as learning and memory. It is more realistic to assume an interactive framework in which different neurotransmitter systems are involved in these cognitive processes.

Indeed, the literature suggests that excitatory amino acids are more important in the formation of memory than Ach, especially glutamate, the most abundant endogenous excitatory amino acid in the brain (McEntee and Mair, 1980). Moreover, the (mesotelencephalic) dopaminergic system has been proposed to be functionally related to the convergence of information about reward (the prefrontal cortex and amygdale) and visual processing and attention (neocortical input to striatum) (Dunnett and Robbins, 1992). Noradrenaline, a neurotransmitter localised in pathways projecting to the cortex, is also thought to be involved in the process of selective attention. Serotonin is another neurotransmitter that has been linked with alcohol dependency. Notably, the noradrenergic and serotonergic systems have been implicated in the physiological pathway of the Korsakoff syndrome (McEntee and Mair, 1980); indeed, it has been reported that fluvoxamine (Martin et al. 1986) and clonidine (Mair et al. 1986) both improve the Korsakoff state.

Furthermore, also the location of the lesion(s) responsible for the amnesia in Korsakoff psychosis is not completely known. In addition to the BFCN (Cullen et al. 1997), several neuroanatomical regions have been examined in a number of detailed neuropathological studies. These regions include the hippocampus (Harding et al. 1997) the dorsolateral prefrontal cerebral cortex (Kril et al. 1997) the brainstem serotonergic nuclei (Halliday et al. 1993) the noradrenergic locus coeruleus (Halliday et al. 1992) and the vasopressin-containing neurons in the hypothalamus (Harding et al. 1996). No difference was found between amnesic and non-amnesic alcoholics with WKS in any of these regions. Exclusively the

neuronal loss in the anterior thalamic nuclei was found consistently in alcoholic Korsakoff psychosis (Harding et al. 2000).

Taken together, all these findings and the results of the present study do not seem to support a critical role for the cholinergic system in memory loss in WKS, and make it difficult to accept completely the hypothesis that BFCN degeneration is a necessary prerequisite for the memory deficits associated with WKS. Multiple neurochemical abnormalities probably underlie this amnesic syndrome; functional interactions between cholinergic and noncholinergic neuromodulatory systems that are affected in this disease should be further investigated.

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